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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,832	06/07/2001	Jean-Damien Charrier	VPI/00-117	9982
27916	7590	11/25/2005	EXAMINER	
VERTEX PHARMACEUTICALS INC. 130 WAVERLY STREET CAMBRIDGE, MA 02139-4242			BALASUBRAMANIAN, VENKATARAMAN	
			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 11/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/877,832

Applicant(s)

CHARRIER ET AL.

Examiner

Venkataraman Balasubramanian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,8,9,11,12 and 14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-6,11 and 12 is/are allowed.
- 6) ☒ Claim(s) 8, 9 and 14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicants' response, which included cancellation of claims 7, 10, 13, addition of new claim 14 and amendment to claims 8 and 9 is made of record.

Claims 1-6, 8, 9, 11, 12 and 14 are now pending.

In view of applicants' response, the following apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preserving cells or organs or treating arthritis with the instant compound, does not reasonably provide enablement for various diseases embraced in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is same as made in the previous office action and these claims remain rejected for reasons of record.

Applicants' argument presented in the previous response to overcome this rejection with volume of references, which merely show desirability of inhibiting caspase activity to regulate inflammation, does not obviate this rejection, as they have not shown direct nexus between each disease claimed in long list of diseases and classes of disease and caspase activity recited in these claims.

Furthermore, reading some of these references particularly the conclusion section appears to imply that these studies are still at experimental stage, needs further studies. Based on these it appears that substantiation of utility and its scope requirement when utility is "speculative", "sufficiently unusual" or not provided, is still not met with. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support in vivo uses.

In addition, some of the references cited extend well beyond the date of filing of instant application and it is not possible to select which are prior art and which are not as presented.

Finally, applicants should note that this rejection is scope of enablement rejection and hence all diseases embraced in these claims so generically need to be analyzed for enablement requirement.

This rejection is same as made in the previous office action. Applicants' have not addressed the issues or provide evidence that a single class of compound based on the mode of action is useful for treating any or all diseases as embraced in the instant method claims.

Hence this rejection is proper and is maintained.

As for newly added claim 14, the same reasons for lack of scope of enablement applied previously are still applicable. To restate;

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preserving cells or organs or treating arthritis with

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the instant compound, does not reasonably provide enablement for various diseases embraced in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant method of use claim 14 is a Reach through Claim. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions for which they lack written description and enabling disclosure in the specification.

In the instant case, it appears that, because the instant compounds inhibit caspase activity, it is implied that, based on cell inhibition of caspase, any or all diseases can be treated with the instant compounds for which there is no adequate written description and enabling disclosure.

The instant compounds are disclosed to have caspase activity and it is recited that the instant compounds are useful, besides in preserving cells and organs, are useful for all or any diseases including those yet to be discovered as due to caspase for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the inhibition of interleukin-12 overproduction of provided in the specification at pages 14-18. The instant compounds are disclosed to have inhibiting caspase activity and it is recited that the instant compounds, at the time of the instant invention, are therefore useful in treating any or all diseases where caspase is implicated, for which applicants provide no competent evidence. From the reading of specification, it appears that the

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applicants are asserting that the embraced compounds because of their mode action which involves inhibition of caspase activity would be useful for all sorts of diseases including inflammatory diseases autoimmune diseases, bone diseases, proliferative diseases, degenerative diseases sepsis, psoriasis, rheumatoid arthritis, multiple sclerosis etc. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host- warm blooded animal. The fact that a single class of compounds can treat all diseases is incredible and applicants have not provided any supporting evidence or enabling disclosure. Moreover many if not most of diseases such as Alzheimer's disease, multiple sclerosis, Parkinson's disease HIV etc. are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition".

No compound has ever been found to treat disease of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine. Currently, it is beyond the skill of physician today to get an agent to be effective against all diseases.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support

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in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001, wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating a condition or disease related caspase activity.

2) The state of the prior art: The publications cited in the Information Disclosure Statement, expressed, at the time of the instant invention was made, that treating disease by the inhibition of caspase is still exploratory.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely

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with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of inhibiting caspase are unpredictable and at best limited to modulation of arthritis.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related caspase activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or

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use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Allowable Subject Matter

Claims 1-6 and 11-12 would be allowed barring finding of any prior art in a subsequent search. Said claims would be allowable as prior art search in the related area did not teach or suggest instant compounds, composition and method of use embraced in these claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 272-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

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